REMARKS

The above amendments and remarks following this paragraph are the same as those submitted with the Reply After Final Rejection filed March 22, 2007. This paragraph addresses the Advisory Action mailed April 3, 2007. Therein, these amendments were denied entry because they were alleged to raise new issues and introduce new matter. Specifically, it was alleged that the documents submitted by applicants for identifying chemical names for the PDE-IV inhibitors listed in claim 1, were sufficient for all of the compounds except one. It was alleged there was no support provided for naming "tofimilast" and connecting it with either of the CP-325 or CP-366 compounds. Applicants respectfully submit that they filed a document supporting the known chemical name for "CP-325366" being "tofimilast" with their previous Reply filed October 25, 2006. (The initial Reply After Final referred to the "previous support provided' in addition to the new documents.) Attached is a further copy of the tofimilast document, "Drug Report." One of ordinary skill in the art would have known that applicants' recitation of "CP-325,366" was the same as "CP-325366" and that these identify a single compound. Such identifying term was a well known name in this art for this known PDE-IV inhibitor. Further, one of ordinary skill in the art would have known that "tofimilast" is synonymous with this term. Thus, this amendment and the other amendments providing common names or chemical names in place of the synonymous alphanumeric names do not introduce new matter or raise new issues. Applicants, thus, strongly urge that the above amendments be entered and the below remarks be fully reconsidered.

The Amendments

Claims 1 and 7 are amended to replace the chemical alphanumeric identifier with the full chemical name or common name. The amendment is supported by the common knowledge of these synonymous names in the art. Support therefore is found in the previously provided literature references. The amendments do not narrow the broadest scope of the claims.

It is submitted that the above amendments would put the application in condition for allowance or materially reduce or simplify the issues for appeal since they render moot the 35 U.S.C. §112, second paragraph rejection. The amendments do not raise new issues or present new matter and do not present additional claims. The amendments have been made to render

the 35 U.S.C. §112, second paragraph, rejection moot. As discussed below, they were not believed to be necessary but are made to advance prosecution and have no substantive effect. Thus, they were not earlier presented. Accordingly, it is submitted that the requested amendments should be entered.

Applicants reserve the right to file one or more continuing and/or divisional applications directed to any subject matter disclosed in the application which has been canceled by any of the above amendments.

The Rejection under 35 U.S.C. §112, second paragraph

The rejection of claims 1, 2, 4, 5, 7-11, 13, 19-38, 43 and 44 under 35 U.S.C. §112, second paragraph, is respectfully traversed.

Although applicants remain of the opinion that the previously recited identifiers of the specific PDE-IV inhibitors were well-defined, permanent and would have been known to one of ordinary skill in the art, they have been replaced with either the chemical name or the common name by which they are otherwise known in the art. Thus, it is believed that the rejection is rendered moot and should be withdrawn.

The Rejection under 35 U.S.C. §103

The rejection of claims 1, 2, 4, 5, 7-11, 13, 19-38, 43 and 44 under 35 U.S.C. §103, as being obvious over Knowles (WO 03/011274) in view of Meissner (U.S. Patent No. 6,706,726) further in view of Hill (U.S. Patent No. 6,060,069) is respectfully traversed.

Applicants respectfully disagree that tiotropium disclosed in Knowles and applicants' compound 1 are of such similar structure that one of ordinary skill in the art would consider them to have the same or similar properties and be interchangeable. Referring to the formulae shown on page 9 of the Office Action, it is seen that there are five significant structural differences between these compounds:

1) - the functional -OH group in tiotropium is replaced with a methyl group,

2) & 3) - each of two 5-membered rings are replaced with 6-membered rings, and

4) & 5) - in each of these two rings, the sulfur hetero group is removed such that heterocyclic rings are not provided.

There is no basis on the record to assume that such significant changes would not effect the properties of the compound and that these compounds would be interchangeably useful. To the contrary, it is pointed out that tiotropium was known in the art before the Meissner patent

was obtained and Meissner obtained the patent with claims covering compounds of formula I in view of this knowledge. Thus, a determination was made that compounds, such as formula I, particularly with two phenyl groups, were patentably distinct over compounds such as tiotropium, having two thiophene groups. In any event, the number of structural differences, on its face, is such that no presumption can be made that the compounds would have the same or similar properties. Such presumptions, in previous case law, were only made where the structures were adjacent homologs, such as methyl to ethyl. That is certainly not the case here. There is no legal basis to make such presumption where the structures have multiple and significant distinctions as here, i.e., replacing -OH with methyl and replacing each of two thiophene rings with phenyl rings.

The argument in the Office Action that tiotropium is closer in structure to applicants' formula 1 than the other compounds more specifically pointed out by Knowles supports using applicants' formula 1 compound as the anticholinergic in Knowles is not convincing. Even if it were true that tiotropium is closer to formula 1 than the other Knowles compounds (which is not admitted), this in no way supports that tiotropium is sufficiently closely similar to applicants' formula 1 compound that one of ordinary skill in the art would expect them to have the same or similar properties and be interchangeable.

Furthermore, Knowles only mentions tiotropium in a long list of other compounds and does not specifically direct one of ordinary skill in the art to select this compound over the other ones. To the contrary, Knowles directs one of ordinary skill in the art towards other compounds which are even more structurally distinct from applicants' formula 1; see, e.g., page 4, line 28, to page 5, line 31, and applicants' previous Reply (which is incorporated by reference herein). Thus, rather than suggesting replacement of its compounds with the Meissner compounds, Knowles directs one of ordinary skill in the art towards selection of the compounds which are alleged in the Office Action to be even more structurally distinct. In view of these teachings in Knowles one of ordinary skill in the art would be directed away from compounds of applicants' formula 1, rather than towards them.

Additionally, Meissner further directs one of ordinary skill in the art away from interchanging such compounds and away from an expectation that such compounds would exhibit the same or similar properties. Meissner refers to compounds of the type disclosed as anticholinergics in Knowles in its Background section (col. 1, line 33, to col. 2, line 26) and discloses that such compounds are deficient in meeting the requirements desired for the

Meissner invention. Thus, Meissner's invention is directed to its structurally distinct compounds with distinct properties.

Additionally, Knowles teaches that a specific type of anticholinergic is desired which has a certain M_1 and M_2 receptor antagonist activity; see paragraph bridging pages 4-5 of Knowles. Meissner provides no disclosure either way as to whether its compounds possess such antagonist activity. Thus, whether or not the compounds actually possess such activity, the failure of Meissner to teach such activity further detracts from any reasonable expectation of success by one of ordinary skill in the art in substituting the Meissner compounds, particularly selecting the specific compound of Example 1, into the Knowles compositions. This argument was made by applicants in their previous Reply but was not addressed in the Final action. Applicants thus reemphasize this argumentand urge full consideration.

Applicants therefore urge that the cited references are directly contrary to the presumption which is made as the basis for the rejection, i.e., that the Meissner anticholinergics could be substituted for the Knowles anticholinergics with the expectation that the same or similar properties would be obtained.

Further directing one of ordinary skill in the art away from applicants' invention is the fact that Meissner does not suggest the use of its anticholinergics of formula 1 together with PDE-4 inhibitors.

Additionally, Knowles does not direct one of ordinary skill in the art to select the particular PDE-4 inhibitors recited in the instant claims. Knowles, instead, particularly directs one of ordinary skill in the art towards those having a selective activity, specifically cilomilast or Ariflo®; see, e.g., page 3, line 25, through page 4, line 27. see, e.g., page 4, line 28, to page 5, line 31.

In view of all of the above, applicants strongly urge that the cited prior art does not provide a reasonable suggestion to one of ordinary skill in the art to make the particular combination of a compound of formula **1** of the instant claims together with a specific PDE-4 inhibitor, as recited in claim 1. To the contrary, the teachings of the references considered as a whole would have pointed one of ordinary skill in the art away from making such specific combination. Thus, it is urged that the combined teachings of Knowles and Meissner fail to suggest the claimed invention to one of ordinary skill in the art.

Hill was relied upon in the Office Action for suggesting certain dependent claim embodiments regarding particular excipients in the compositions. Hill provides no suggestions to make up for the deficiencies of the combination of Knowles and Meissner

discussed above. Hill provides no suggestion of combining a compound of Meissner's formula 1 as an anticholinergic in the PDE-4 inhibitor compositions of Knowles. Therefore, while applicants reserve the right to discuss the distinction of the combined teachings of Hill for such dependent claim features, such discussion is not believed to be necessary at this time to establish nonobviousness.

For all of the above reasons, it is respectfully submitted that the combined teachings of Knowles, Meissner and Hill fail to suggest the claimed invention to one of ordinary skill in the art. Thus, the rejection under 35 U.S.C. §103 should be withdrawn.

The Provisional Obviousness-type Double Patenting Rejections

The provisional obviousness-type double patenting rejection of claims 1, 2, 4, 5, 7 and 43 over claims 1-13 of US Ser. No. 10/613,783 in view of claims 1-8, 11 and 21-23 of U.S. Patent No. 6,706,726 is overcome by the terminal disclaimer previously filed herein.

It is submitted that the application is in condition for allowance. But the Examiner is kindly invited to contact the undersigned to discuss any unresolved matters.

Respectfully submitted,

/John A. Sopp/
John A. Sopp, Reg. No. 33,103
Attorney/Agent for Applicants

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

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JAS:cak